UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/267,511	03/12/99	BRENNEMAN	D 015280-37700

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TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO CA 94111-3834

EXAMINER	
TURNER, S	
ART UNIT	PAPER NUMBER
1647	15

DATE MAILED: 06/29/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/267,511	Brenneman
Examiner	**Art Unit**
Sharon L. Turner, Ph.D.	1647

-- Th MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 4-23-01

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-44 is/are pending in the applica

4a) Of the above, claim(s) 19-44 is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-18 is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims 1-44 are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☐ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 12

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

Response to Amendment

1. The amendment filed 4-23-01 has been entered into the record and has been fully considered.

2. As a result of applicants amendment, all rejections not reiterated herein have been withdrawn by the examiner.

3. Claims 1-44 are pending.

4. Claims 19-44 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10.

Rejections Necessitated by Amendment

Sequence Requirements

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR 1.821 - 1.825) before the application can be examined under 35 U.S.C. §§ 131 and 132.

In particular, the examiner notes that the newly amended sequences in elements (d)-(f) of claim 1 lacks reference to an identified SEQ ID NO as required by the sequence rules.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-2 and 12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Applicants claims as amended introduce elements (d)-(f) which recite full length ADNF I and III polypeptides without reference for that which constitutes full length ADNF I and III polypeptides.

The specification discloses SEQ ID NO's:1-2 and 21-26 which correspond respectively to the ADNF amino acid sequences. These SEQ ID NO's meet the written description provisions of 35 USC 112, first paragraph. However, the claims are directed to or encompass corresponding sequences from other species, mutated sequences, allelic variants, splice variants and combinations thereof. None of these sequences meets the written description provision of 35 USC 112, first paragraph.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that, "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is for purposes of the 'written description' inquiry, whatever is now claimed." (See Vas-Cath at page 1116.)

With the exception of SEQ ID NO's:1-2 and 21-26 of the instant application, the skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic and amino acids and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The specific nucleic and amino acids are required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.

Therefore, only SEQ ID NO's:1-2 and 21-26 , but not the full breadth of claims meet the written description provision of 35 USC 112, first paragraph. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.)

Applicants argue that the claims properly define a genus of peptides and reference WO96/11948, US Patent 6,174,862, WO98/35042 and US application 09/187,330 to provide written description for the genus of ADNF I and III peptides including full length.

Applicants arguments filed 4-23-01 have been fully considered but are not persuasive because instant application fails to properly incorporate by reference those species of molecules which represent full length ADNF I and III polypeptides and which are required to fulfill the description of the genus, specifically with respect to the recitation of full length molecules.

8. Claims 1-18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting fetal demise, decreased fetal birth weight, and decreased fetal brain weight in a subject exposed to alcohol in utero comprising administering to the subject an ADNF polypeptide of SEQ ID NO 1, 2 or a mixture of SEQ ID Nos 1 and 2,30 minutes prior to alcohol exposure, does not reasonably provide enablement for reducing the conditions associated with fetal alcohol syndrome, particularly as the claim is drawn to subjects which have already developed fetal alcohol syndrome prior to the administration of the claimed ADNF polypeptides and in particular full length ADNF peptides which are not described. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specifications disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without undue experimentation. The factors relevant to this discussion include the quantity of experimentation necessary, the lack of working examples, the

unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims.

Claims 1-18 are drawn to a method of reducing a condition associated with fetal alcohol syndrome in a subject exposed to alcohol *in utero*. The method comprises administering ADNF polypeptides in an amount sufficient to reduce a condition associated with fetal alcohol syndrome.

However, the specification teaches **pretreatment** of animals with ADNF polypeptides NAP and SAL as specified at pp. 22-23 of the specification, **prior** to exposure with ethyl alcohol. This pretreatment produces significant differences in Fetal Demise, Fetal Weight, and Fetal brain Weight in animals subsequently exposed to alcohol as depicted in Figures 1-3. However, such protocol fails to support a reduction in a condition associated with developed fetal alcohol syndrome in a subject, which syndrome indicates conditions including life long reductions in learning, memory, adaptive response, proper brain formation and coordination. In other words, the specification fails to show that the injected peptides are effective to improve or treat fetal alcohol syndrome conditions which have already developed in a patient contracted *in utero* by exposure to alcohol. The specifications teachings in contrast are directed to the prevention of such development in a patient by treatment prior to alcohol exposure. The experimental animals lack the affliction of fetal alcohol syndrome because the animals lack prior exposure to alcohol. Thus, the specification merely shows that administration of said peptides (as specified pp. 22-23 and Figs 1-3) affect Fetal Demise, Fetal Weight, Fetal brain Weight and VIP mRNA in animals

subsequently exposed to alcohol as compared to controls, which showing is not commensurate in scope with the claimed invention. Therefore, the skilled artisan would require further undue experimentation to determine if such peptide administration is capable of reducing any condition associated with fetal alcohol syndrome as a developed condition in a patient as claimed.

The art teaches that fetal alcohol syndrome and alcohol-related neurodevelopmental disorders are characterized by life-long compromises in learning, memory and adaptive responses, in which to date there are no clinical remedies to recommend for either specific or global fetal alcohol effects, see in particular abstract, Hannigan et al., Neurotoxic. & Teratol., Jan-Feb 2000, 22(1):103-111. In addition, Hannigan et al., caution that the findings in rodents using basic research models to assess the potential of treatments for neurobehavioral effects of prenatal alcohol exposure, and the application of such findings to children may not be straight forward, i.e., they are unpredictable in the art, see in particular abstract. Thus, the specification lacks the guidance required by the skilled artisan to develop and test with reasonable predictability the effects of the claimed peptides in fetal alcohol syndrome including compromises in learning, memory and adaptive responses.

Further, with regard to applicants limitation "in an amount sufficient to reduce the condition associated with fetal alcohol syndrome", the claims fail to specify any amount in correlation to any specified condition associated with fetal alcohol syndrome. Thus, the skilled artisan would require further undue experimentation to define suitable conditions which may be affected in fetal alcohol syndrome and to determine the amount of ADNF required to produce

such effects for any of the specified conditions which are not described such that the artisan can recognize the effects, conditions or quantities required..

In addition, the skilled artisan recognizes the unpredictability in the art associated with the prediction of peptide function based upon divergent structure, see in particular Skolnick et al., Trends in Biotech 18(1):34-39, 2000, abstract and Box 2. Thus, for those divergent peptide structures, the skilled artisan would be required to perform further undue experimentation to discover those ADNF peptides which possess the properties of alleviating any condition associated with fetal alcohol syndrome. In particular it is noted that the description lacks support for the recitation of full length ADNF polypeptides as encompassed in both the generic and specific limitations as recited in claims 1-2.

In regard to claim 14, the skilled artisan recognizes that expression of polypeptides from nucleic acid requires the presence of promoter and expression sequences which direct expression in the host cell in vivo, i.e., the claims are directed to gene therapy. Claim 14 recites administration of nucleic acids in the absence of reference to any specifically exemplified sequences for ADNF encoding nucleic acids and for suitable delivery and expression within the fetus such that a condition associated with fetal alcohol syndrome is reduced. The skilled artisan recognizes the difficulties and unpredictability associated with the development of such in vivo systems for nucleic acid/gene therapy, see in particular Smith AE., Ann. Rev. of Microbiol., 49:807-38, 1995, which teach a wide variety of problems that differ with each potential therapeutic application in the design, production and application of viral vectors, see abstract.

Further, Mahato et al., J. of Drug Targeting, 4(6):337-57, 1997 teach the challenges encountered in the development of the maintenance of proper concentrations and relevant vicinity of nucleic acid drugs for delivery *in vivo*, see in particular abstract. Thus, the skilled artisan would be required to perform further undue experimentation to define the nucleic acids to be delivered and suitable expression systems such that *in vivo* delivery of ADNF is achieved at levels and locales effective to reduce a condition associated with fetal alcohol syndrome. Thus, for these reasons, it would take further undue experimentation on behalf of the skilled artisan to make and to use the claimed invention.

Applicants argue that the specification uses an art accepted model of fetal alcohol syndrome, that the specification provides guidance in Figures 1, 2a, 2b, 3, and at p. 7, lines 17-18 such that the artisan can develop and test the effects of the ADNF polypeptides, that the sufficient amount to reduce the condition need not be recited and that the suitable species of ADNF peptides within the genus peptides of the claims can be determined using the guidance of the specification without undue experimentation and that the specification provides guidance for the in vivo delivery of nucleic acids for gene therapy.

Applicants arguments filed 4-23-01 have been fully considered but are not persuasive. The specifications guidance is limited as set forth previously and as exemplified in for example Figures 1, 2a, 2b and 3. The standard of an enabling disclosure is not the ability to make and test if the invention worked but one of the ability to make and use with a reasonable expectation of success. The prior art and previous rejection highlight multiple factors associated with fetal

alcohol syndrome, the determination of peptide function based upon divergent structure, multiple conditions which occur in fetal alcohol syndrome which vary in prevalence, severity, and scope, the unpredictability in the art of peptide interactions and gene therapy and a lack of guidance in the specification for the amelioration of a generic recitation of fetal alcohol syndrome conditions for which only limited exemplifications are disclosed in the specification. Cumulatively these factors do not support an enabling disclosure for the scope of the generic recitations as claimed.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 1-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-2 are indefinite with respect to the recitations "full length ADNF I" and "full length ADNF III" because such recitations are neither defined nor readily recognized in the art. The metes and bounds of the encompassed polypeptides are indefinite.

Applicants argue that page 6 provides sufficient characterization of the claimed ADNF polypeptides.

Applicants arguments filed 4-23-01 have been fully considered but are not persuasive because p. 6 of the specification fails to disclose that which comprises a "full length ADNF I" or "full length ADNF III" polypeptide as recited in the claims. The skilled artisan can not discern

those structural or functional determinants which are included or excluded from the recitation. Further clarification is required.

Status of Claims

11. No claims are allowed.

Conclusion

12. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

13. Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (703) 308-4242.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sharon L. Turner, Ph.D. whose telephone number is (703) 308-0056. The examiner can normally be reached on Monday-Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached at (703) 308-4623.

Sharon L. Turner, Ph.D.
June 28, 2001

CHRISTINE J. SAOUD
PRIMARY EXAMINER

Christine J. Saoud